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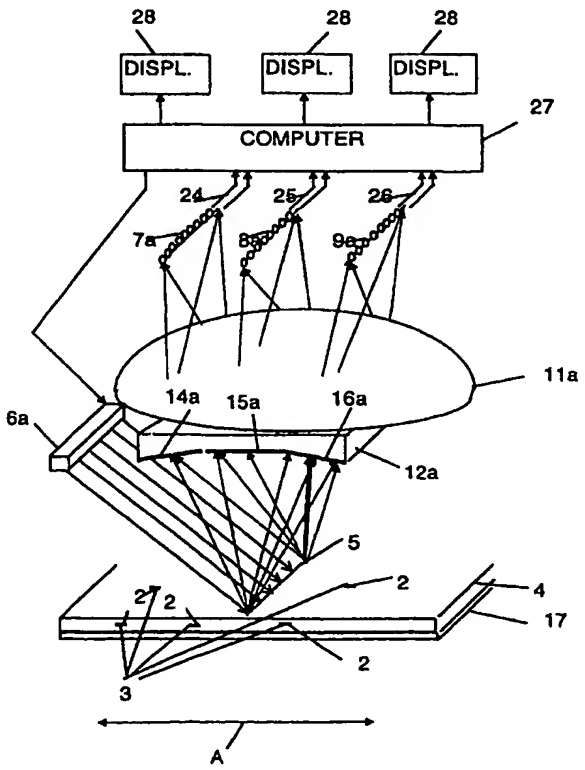
(54) Title: METHOD AND DEVICE FOR MEASURING LABELS IN A CARRIER

(57) Abstract

The invention relates to methods and devices for monitoring an essentially planar carrier having at least one kind of label, preferably at least two, distributed to micro-areas of the carrier (4). The labels have mutually different radiation reacting features providing mutually different radiation features when illuminated. The carrier is illuminated (6; 35 to 40; 45; 46; 47, 48; 50 to 52;53;6,84) with radiation providing reaction of said radiation reacting features of the labels. At least two different, separate features of the emitted fluoresced radiation are detected essentially simultaneously. Values of the features are indicated separately. The separate features are preferably different wavelengths or wavelength bands but different polarisations are also possible. Detector element row(s) (7a, 8a, 9a; 41, 42, 43; 60, 61, 62; 61a) and the carrier (4) are moved in relation to each other whereby the carrier is scanned.



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METHOD AND DEVICE FOR MEASURING LABELS IN A CARRIER.

Technical field

The present invention concerns a method and device for measuring one or more detectable compounds (labels) in micro-areas of an essentially planar carrier (where a micro-area is a sub-area of the surface of the carrier).

In the field of the invention, label(s) has/have been used for assaying the presence/-absence or the amount of a compound/compounds or detecting reaction/reactions the occurrence of an in the micro-areas concerned. See further under the heading "Carriers containing two-dimensional labelled micro-area pattern" in the later part of the specification.

The labels earlier used in the field of the invention have exhibited radiation reacting features and radiation features. Illustrative examples of pairs of radiation reaction features and radiation features are excitation and emission of fluorescent labels, excitation by chemical reactions to give chemi-luminescence, changes in the polarisation of incoming light etc.

There are two previously implemented methodologies for monitoring fluorescently labelled labels that have been separated in a carrier (e.g. by two-dimensional gel electrophoresis) into micro-areas, each of which contain an individual label or a group of labels. One of them is based on point scanning and the other on area scanning. The latter has been commercialised in a gel-imager from Life Science Resources and uses rotatable filter wheels for selecting wave-length bands. See for instance US 4874492.

In the field of the invention there is a general desire to use more than one label in the same carrier.

Some problems with earlier techniques.

In the case where two or more labels of the kind defined above are used in separate carriers, comparisons may be complicated by the fact that the conditions provided in the separate carriers may differ, which means that the conditions must be monitored.

In the case where two or more labels are used in the same carrier, the scanning must be carried out several times to provide a separate record for each of the labels. This is very time-conserving time and often gives inaccurate results.

The area scan system from Life Science Resources is relatively slow and needs mechanical adjustments (rotation of the filter wheels) to be able to investigate more than one light wavelength band. The system also has patching problems, which occur when combining different sub-areas to form one image of the surface of the carrier. It is also difficult to provide an even distribution of exciting light across the carrier surface. This creates problems as the micro-areas are illuminated unequally which influences the radiation emitted from the micro-areas in an uncontrolled way. These two problems, among others, decrease the ability of flat fielding (matching light levels from different images to each other) and therefore reduce the overall sensitivity. It also makes comparisons between different light features inaccurate.

OBJECTS OF THE INVENTION

The main objects of the present invention are to provide improvements with respect to at least one of the features below.

- Fast scanning.
- Monitoring more than two different label features at the same time without mechanical adjustment.
- Flexibility regarding modules used for radiation as well as for detection.

- Integration with other units in order to increase automation around the different parts of system as well as of the entire system, including preparation of gels.
- Facilitating evenly distributed light conditions across the carrier area which is being imaged on the detector.
- Easy to calibrate.
- High resolution and accurate images.

The above-mentioned objects also mean that the inventive device and method also should enable traditional reflectance and transmission measurements with a high performance.

THE INVENTION

A first aspect of the invention is a method for measuring one or more labels in micro-areas present in a two-dimensional pattern in an essentially planar carrier. The most important sub-modes at the priority date are to monitor, for instance:

a) the result of the separation of the labels in one or more samples into individual micro-areas of a carrier, each of said micro-areas containing an individual label or a group of labels; and/or

b) individual results of reactions taking place in each micro-area of a carrier.

The inventive method starts by providing an essentially planar carrier, which exhibits a number of micro-areas arranged in a two-dimensional pattern. The micro-areas may or may not exhibit a label as defined above. There may be at least one kind of label, preferable at least two, in microareas in the carrier. The labels could have different features. The characterising feature is detecting the at least one kind of label in the carrier along at least one line with at least one detector element row for essentially simultaneous detection of at least two different features of the at least one kind of label.

The features monitored may differ with respect to radiation reacting features (for instance excitation by light or by chemical reaction) and/or radiation features (for instance emission) etc. including interaction with polarised light. More particularly the difference may refer to wave-length or wave-length band for either or both of excitation and emission. Difference in time behaviour of fluorescence between different labels is of potential use. In the preferred mode one monitors essentially simultaneously two or more different radiation features (for instance fluorescence emission) corresponding to a respective label in the carrier.

For labels requiring illumination in order to provide radiation features, e.g. fluorescence, one has to radiate/illuminate and micro-areas measure radiation features from label(s) present in the micro-areas of the scanning line essentially simultaneously. This may be accomplished by the arrangement for radiation/-illuminating (the illumination means) described in the context of the device aspect of the invention. See below.

The detector elements could be provided in at least one row for detecting the radiation emitted from labels along at least one line (the scanning line) in the carrier, and for scanning the carrier by moving the line(s) (the scanner head) across the carrier to be monitored in a direction perpendicular to the extension of the line(s). One or more lines in the carrier may be illuminated and the emitted radiation from said lines are detected by a number of parallel rows of detector elements, at least two of the parallel rows detecting mutually different qualities of the emitted radiation. A number of lines in the carrier may be illuminated, and the emitted radiation from each of the lines may be detected by an individual among a number of parallel rows of detectors, each row detecting mutually different qualities of the emitted radiation. The illumination of the line(s) could be made simultaneously with different kinds of radiation providing different radiation reacting features of the labels, and the different detector element rows could indicate different qualities of the emitted radiation. The illumination of the lines could be made in sequence with

different kinds of radiation providing different radiation reacting features of the labels, and the different detector element rows could indicate different qualities of the emitted radiation. The illumination could also be spatially separated, and the different lines could be simultaneously imaged on different detector element rows which also are spatially separated.

Preferably, the radiation and the detector element rows are placed in a fixed arrangement, and a number of carriers are moved in sequence through the fixed arrangement. The signals generated from the detector element rows could be processed separately. The results of the processing are preferably presented on at least one display.

Further details about the method are apparent from the description below.

A second aspect of the invention is a device for monitoring an essentially planar carrier having at least one kind of label, preferable at least two, distributed to micro-areas of the carrier, the labels having different radiation reacting features or radiation features. The device is characterised by comprising:

- illumination arrangement for providing radiation to at least one line of the carrier;
- detector means, comprising at least one detector element row, for detecting at least two of said features in the at least one line in the carrier;
- scanning means for moving said detector element row(s) and said carrier in relation to each other thereby scanning the carrier. An analysing means could be provided for treating the signals received from the at least one detector element row(s) and generating signals representative of the distribution of the at least two detected features from the at least one label in the carrier.

Certain labels, for instance fluorescent labels, require interaction with incoming light, for instance excitation light. In these cases the illumination means will provide radiation of the appropriate kind for the radiation reacting features of each

individual label intended to be used together with the device. The radiation unit and the detector element rows are preferably placed in a fixed arrangement so that they are forced to describe the same movement relative the carrier surface, when the carrier surface is being linearly scanned by the detector. The illumination means can also be located so as to guide the radiation into the gel through an edge at one side of the gel.

The radiation unit will typically provide radiation across a line on the carrier to be monitored. In the case that labels exhibiting different kinds of radiation reacting features are to be used, then the radiation unit should enable the appropriate kinds of illuminating features to reach each line of microareas when they are being imaged by the proper detector element row.

The linear scanning movement of the linear detector may have various directions, for instance perpendicular to the straight line defined above or circular. In the former case the linear detector preferably covers the breadth or length of the carrier surface. In the latter case the circular movement may be around the centre of the carrier surface. The centre of, or one end of, a linear detector element row is preferably located at the centre of the carrier surface. By the term "one end of a linear detector element row" is also included that the end may be an extension which does not comprise any functional detector element but which is still located at the centre of the circular movement. In variants utilising circular scanning, the detector element rows are preferably directed radially from the centre of the circular scanning movement, i.e. they are not parallel in this case. In these latter variants non-parallelity also applies to other linear arrangements around the detector element rows, which are intended to follow the scanning movement of the detector element row. See the drawings.

The most important scanning movements are to keep the linear scanner fixed and to move the carrier or vice versa, with a preference for the former.

The term "carrier surface" is primarily referring to the part of the surface of the carrier on which there are micro-areas to be scanned.

The device will be able to capture one or more linear images of the carrier substantially simultaneous. The images will be captured in the same scan with aspects of different light features of the labels and will provide at least one image comprising information of these different properties, which information can be used for further analysis.

The generated image(s) will not be segmented because of the use of one or more linear detector element for the scan as opposed to what would be the case of segmentation with use of an area detector. The system will be easy to calibrate as the line can be calibrated on a line which then will be representative for all of the scans as long as the scanner unit and the radiation unit are not moved with respect to each other.

ADVANTAGES OF THE INVENTION

- Fast scanning primarily enabled by detector elements working in parallel.
- Monitoring more than two different label features simultaneously in the same scan primarily enabled by providing separated detector element rows, each row having a different imaging feature. However, an essential simultaneous scan could be provided by having a sequence of lighting and detecting, e.g. by the same detector element row, at all the instances during the scan when a measurement is performed.
- Flexibility regarding modules used for radiation as well as for detection. Primarily enabled by low price and easy adjustment of linear detectors and light sources.

- Integration with other units is primarily enabled by transportation of the carrier in the imaging system.
- Facilitating evenly distributed light conditions is primarily due to the fact that even distribution of light across a line is much easier to achieve compared to across a whole area.
- Calibration has only to be performed across one line and is then applied across all the lines in the image.
- High resolution and accurate images are enabled by the possibility in the invention to use small pixel size and qualities of linear detectors. The image quality is also improved by the fact of easy calibration.

BRIEF DESCRIPTION OF THE DRAWINGS

For a more complete understanding of the present invention and for further objects and advantages thereof, reference is now made to the following description taken in conjunction with the accompanying drawings.

As a matter of convenience, the drawings show the invention adapted to monitoring the result of a separation of a mixture of protein labels using two-dimensional gel electrophoresis. The various protein labels of a mixture (a sample) are dyed (labelled) with a fluorescent dye prior to the separation. A variant in which two or more mixtures of proteins corresponding to different samples are dyed with a respective fluorescent dye, then mixed and separated, is also expressly encompassed by the drawings.

FIG. 1 shows schematically a first embodiment of the invention having a first embodiment of illuminating dyed labels of a sample in the carrier. The discussion refers to dyeing with one or more dyes.

FIG. 2 shows schematically a second embodiment;

FIG. 3 shows schematically an alternative arrangement with the detector optics using a folding mirror.

FIG 4 shows schematically another embodiment of the light source.

FIG. 5 shows schematically another embodiment of the inside of the scanner head comprising detector element rows and optical filters.

FIG. 6 shows schematically an embodiment with a light source from above the carrier.

FIG. 7 shows schematically an embodiment with a light source from below the carrier.

FIG. 8 shows schematically a first embodiment to provide a line of light across the carrier by scanning a point of light.

FIG. 9 shows schematically a second embodiment to provide a line of light across the carrier by using a line generating optical arrangement.

FIG. 10 shows schematically a third embodiment of the invention.

FIG. 11A and 11B show schematically another two embodiments of the detector element rows, the detector optics, and the radiation sources.

FIG. 12 shows schematically still another embodiment of the detector and detector optics arrangement.

FIG. 13 shows schematically a way to easily combine the invention with different other units to increase automation.

DETAILED DESCRIPTION OF EMBODIMENTS

As seen in the embodiment shown in FIG 1, a scanner head images the different labels 2 of a sample 3. The sample can be provided in a 2D-carrier 4, for instance a 2D electrophoresis gel. A thin line 5 across the sample, is illuminated by a light source 6a, hereby exciting the dye coupled to the labels 2. The light source 6a is shown to be elongated in this embodiment. The line 5 is to be imagined onto a number of parallel detector element rows 7a, 8a, 9a (for example three) by means of optics 11a, 12a. The light of the light source 6a is chosen such that the dye(s)

coupled to the labels 2 is (are) excited. The scanning is provided in the direction of the arrow A. Either the carrier 4 or the scanner head comprising the optics and detector element rows together with the light source 6a can be moved.

The light source 6a illuminates the separated labels 2 of the sample/samples 3 in the carrier 4 providing light with specific properties, for example in a defined wavelength band or defined wavebands, and thus produces radiation which activates a fluorescent process in the separated labels 2 of the sample/samples so that they emit light with different properties to that what is emitted by the light source 6a. It is thus to be noted that it is possible to have a light source emitting light having only one specific property, to which several of the labels react in different ways, each way representing emitted light of a special kind and directable to one separate detector element row, or a light source having different specific properties to which each kind of label reacts in a different way.

Each of the detector element rows 7a, 8a, 9a is adapted to detect an individual feature of light, such as individual wavelengths or wavelength bands of, for example, fluorescence marked labels 2. It is also possible to use detector arrangements detecting different kinds of polarisations.

The light emitted from the monitored line 5 on the carrier 4 is focused onto the detector element rows by the detector optics which is adjusted such that the light arriving at the detector element rows can be registered with aspects to the different properties of the light on each detector element row 7a, 8a, 9a separately. The optics can then comprise an ordinary, circular camera lens 11a provided with an elongated prism 12a on its side turned towards the carrier 4. It is to be noted that the lens is ordinary in principle but should preferably be a high performance macro lens.

The prism 12a is illustrated as being positioned a little distance away from the lens, but it is preferably positioned directly onto the surface of the lens. The prism 12a is shown to have three zones having different obliquity.

The prism 12a will refract the light so that the same line 5 is imaged on the different detector element rows 7a, 8a, 9a simultaneously. The prism 12a can be provided with different kinds of arrangements 14a, 15a, 16a individually for each zone surface of the prism 12a. Such arrangements could be filters (illustrated with thick lines) on the prism 12a for capturing different wavelength properties of the line 5 on the carrier 4. Other kinds of arrangements will be described below.

As will be illustrated later on in FIG 11A, different lines on the carrier can be imagined on the different rows of detector elements and then no prism provided on or at the lens is needed.

The carrier 4 with the separated labels 2 of the sample/samples 3 to be monitored could, for example, be provided on a plastic film or a glass plate 17 which thus is covered with the carrier 4. The separated labels 2 can be dyed with fluorescent dyes with different properties for the different samples 3 to be monitored in the same carrier 4. However, it is to be noted that the labels sometimes could be fluorescent themselves or adapted in another way so as to be able to be monitored separately and then they do not have to be dyed.

For all the embodiments of the invention, the signals from the detector element rows 7a, 8a, 9a are analogue/digital-converted (not shown) and fed separately 24, 25, 26 to a computing device 27 which could add signals from detectors catching the same features using information about the scanning motion to generate at least one image and which processes the signals originating from separate detectors or detector element rows 7a, 8a, 9a catching different features separately.

The processed signals can be fed to generate a separate image of each feature or an image containing information of all the different features. The images can be displayed separately or together on the same display (not shown) or on several displays 28. The images can be analysed by any software adjusted to image process the images generated by the scanning device, as is apparent for the person skilled in the art. However, other kinds of signal processing of the signals from the individual detector elements are also possible, as is apparent for a person skilled in the art. The way of analysing is not a part of the actual invention and will therefore not be discussed.

In the embodiment shown in FIG 2, a number of detector element sub-housings 1 image the different labels 2 of a sample 3 in a carrier 4. The carrier is illuminated with a light source arrangement 6 providing light on the carrier 4.

The sub-housings 1 are provided in a row. The carrier is illuminated along a line 5, parallel to the row of scanner sub-housings on the carrier 4, with a row of light sources 6 in this embodiment. Either the carrier 4 or the row of sub-housings 1 together with the light sources 6 can be moved.

The light sources 6 in the arrangement could, for example, be lasers that can provide well defined light beams on the carrier 4. The light sources 6 can be placed in different positions thus rendering light on the carrier from different directions as will be apparent from other embodiments described below. In FIG 2, the light beams are illuminating the line 5 on the gel obliquely from above. Since all the sub-housings 1 have a similar design, each of the individual kinds of the single detector elements 10, 11, 12 belonging to the different sub-housings is presented in a row extended parallel to the line 5. Each sub-housing 1 has its own optics comprising a lens 8 and a prism device 13 having filters and adapted to provide each of the single detector elements 10, 11, 12 in each sub-housing with radiation emanating from the dyed labels of the sample 3.

In FIG 2, the sub-housings 1 are illustrated to be separate from each other, but it is to be noted that it is not necessary to have separating walls between them. This means that they can be provided in one and the same detector element housing.

In one variant, commonly used in so-called fax arrays, there are one or more housings, each of which comprises one or more detector element rows defining a common scanning line in the carrier, an irradiation arrangement for providing radiation onto the scanning line fitting the radiation reacting feature of a label/dye used and means for directing radiation from the scanning line to the detector element row(s). Two or more housings of this type detecting radiation from different labels/dyes may be used in parallel, i.e. the irradiation differs between the housings, for instance with respect to wavelengths. Housings adapted to detect radiation from the same label/dye may also be used in parallel.

As seen in FIG 3, the detector element housing 31 can image the carrier 4 through an oblique mirror 32 (in the figure being at 45°) thus rendering a more compact device. Also shown in FIG 3, the light source 30, preferably here a laser, can be coupled in through the side of the carrier 4 thus providing a line of light internally in the carrier along the line 5 which is imaged on different detector element rows in the detector element housing 31 lying on one side. The detector elements could be arranged in the same way as for the detector element rows in FIG 1. The light source 30 excites the separated labels 2 provided along this line 5 since it is provided as a line of light inside the carrier 4.

As illustrated in FIG 4, the light source arrangement for the different wavelengths could instead be several light sources positioned in rows, one row for each colour/wavelength. Wavelength filters may be placed in front of the light sources instead of having particular light sources for each desired wavelength. FIG 4 shows light source rows 35, 36, 37 having elongated filters 38, 39, 40, respectively, placed

under each light source row. With this arrangement it is possible to have the same kind of broad spectral light sources everywhere, or elongated light sources (not shown). It is in some designs suitable to light one kind of light source separately, such that the different kinds are switched on in sequence. However, in this embodiment a multitude of light sources could be lit simultaneously.

The separation between the light emitted by the light source arrangement and the light output from the dyes is, besides by geometrical optics, further improved by filtering. The fluorescence to be detected could have different characteristics, for example, spectral characteristics, emitting light of certain wavelength bands.

FIG 5 illustrates an embodiment of a detector head arrangement or housing where each detector element row 41, 42, 43 of detector elements is provided with a filter 41', 42', 43', respectively, each having a passband around a wavelength adapted to the colour to be registered by the row. The signals from different kinds of detector elements, adapted to the light sources, may be recorded in sequence. The sequence cycle is then very short, so that in practice it could be regarded that the different wavelengths emitted from one and the same line are recorded simultaneously, i.e. without significant linear movement of the detector housing before the light features of the next line of micro-areas are recorded.

The colour of the light source can, for increase sensitivity when detecting, for instance, fluorescence, be filtered from the light output from the dyed labels. The fluorescence to be detected could have different spectral characteristics depending on the dyes used. The detector elements in the detector housing, if required in combination with different light sources, are intended to detect at least two different kinds of light features simultaneously, i.e. as many kinds of features the linear detector has detector element rows detecting different radiation features and light source rows corresponding to radiation reaction features resulting in said radiation features. The number of detector element rows reacting on different light features is

only limited by practical considerations from case to case. The different features are principally different wavelength bands, but it could also be useful to detect different polarisations and other features, such as time behaviour.

It is to be noted that the light source can have different designs and be placed in different positions thus rendering light on the carrier 4 from different directions, for example from above, as illustrated by an elongated illuminating device 45 in FIG 6, from below from an elongated illuminating device 46 in FIG 7, or by a scanning device 47 connected to a single light source 48, or some light sources in a narrow group, obliquely from above in FIG 8.

Thus light, as shown in FIGs 1, 2, 6, 7, 8, 11 does not necessary have to be provided in a straight angle from the carrier but rather at a skew angle as shown in FIGs 1, 2, 8 and 11 thus using the geometry to avoid direct reflection of light to the detector element rows in the scanner head arrangements 1 (or common housing) and to decrease dark-levels on the detector elements, and to increase the relative sensitivity of the detector elements. The light can be provided across the line 5 of the carrier 4 from the different possible positions. There are multitudes of possibilities to arrange the scanner head arrangement 1 using different sets of detector elements 10, 11, 12 and detector optics 8.

In order to provide excitation light particularly adapted to the dyes used it is possible, as illustrated with dotted lines in FIG 2, to have several light sources 6, for instance one per detector element row, each light source 6 emitting light with individual properties adapted to cause a reaction of an individual among the dyes.

The light source can be provided with line generating optics 45, as illustrated in FIG 6. As suggested in FIGs 6 and 7 the light source 45, 46, respectively can be extended in space itself, for example as illustrated in FIG 9, by consisting of a row of individual sub-light sources, e.g. LED (Light Emitting Diodes) 50 to 50'''',

provided with for example a filter 51 for controlling the properties of the light and a lens 52 for focusing the light to the actual line 5 on the carrier 4 which is currently to be monitored. The extended light source 50 to 50'''' could also be a linear lamp of any kind. It is possible to let the different sub sources 50, 50', 50'',.... have individually different properties.

The light from each light source 50 to 50'''' must be separated from the light output of the dyes used in the case fluorescence is detected. This is partly done using geometry and skew angles to avoid reflections and decreasing dark-levels as discussed earlier.

As shown in FIG 10, each light source 53 emits light 54 on a line 5 on the carrier 4. When a label 2 of the sample 3 showing fluorescent behaviour is hit by the light 54 it absorbs the light, and then re-emits light 55 of different properties than the absorbed light 54. The light re-emitted by the fluorescent process is spread in all directions and therefore also in the direction 55' towards the detector element housing 56 to be recorded.

The detector element housing 56 is intended to detect at least two different kinds of light features.

FIG 11A is similar to FIG 1 except that the three rows of detector elements 60, 61, 62 image three different lines 68, 69, 70 onto the three detector element rows 60, 61, 62. The detector optics 64 is adjusted so that the light to the different detector element rows 61, 62, 63 can be registered separately with aspects of different properties of the light. This can be performed through arranging a separate filter 65, 66, 67 in front of each detector element row, as shown in FIG 5, or by providing detector optics 64, as illustrated in FIG 1 where a prism 12a is placed in front of the detector optics. Thus, it is possible to use a detector optics that images three, or less or more, different lines 68, 69, 70 on the carrier to the detector element rows 60, 61,

63 through different filters 65, 66, 67. The image of the monitored separated labels 2 of the sample/samples 3 in the carrier 4 is then corrected in a later analysis. It is possible to perform this correction since the distance between the different lines 68, 69, 70 on the carrier 4 is well known and so is the scan movement. The different lines are thus illuminated by different light sources 68a, 69a, 70a with different features, such as by different LED rows.

In FIG 11B there are three different light sources 68a, 69a and 70a irradiating in sequence three physically separated scanning lines 68, 69, 70 with a respective radiation adapted to the radiation reacting features of a respective label/dye. The radiation from the respective scanning line is deflected by a prism 64a such that it via the lens means 64 is directed to the same common detector element row 61a. During the period of time required for one cycle of irradiation of, and measuring radiation from, each scanning line 68, 69, and 70, the scanning lines are not moved forward to any significant degree. In this variant labels/dyes having the same radiation features but different radiation reacting features may be used.

It is also possible to not provide the detector optics with a prism but to use separate detector optics 71, 72, 73, as illustrated in FIG 12. Each detector optics 71, 72, 73 is provided with filters 74, 75, 76 belonging to a separate detector element row 77, 78, 79, as discussed above. In the embodiment shown, the optics are adapted to focus the same line 5 onto the different detectors but it is apparent that they also can be adapted to focus mutually separate lines onto the different rows of the detectors, as in FIG 11A.

Referring to all the embodiments, it is to be noted that, even though three detector element rows are shown, there could be only one, or two, or more than three, detector element rows.

As in all embodiments discussed above, the scanner head or housing together with the light source/sources, and the carrier 4 are moved in relation to each other. The scanning over the carrier, monitoring the individual micro-areas for presence/-absence or amounts of the dyes used, could preferably be done by a scanner head having a fixed position and a carrier 4, which is moved. The movement of the carrier 4 could be constant and the detector element rows be controlled to record light features from the individual micro-areas in the carrier 4 at intervals integrating over a period of the scan movement. It is also possible to move the carrier 4 stepwise between the records.

It is to be noted that the movement does not have to be linear but could, for example, be circular. The scanning line 5 on the carrier 4 is essentially perpendicular to the sequential placement of the detector element rows and therefor parallel to the extension of the separate detector element rows, as they appear in the Figures.

The monitoring device in the embodiments discussed above thus comprises at least one linear array scanner, and the detector elements in at least two detector element rows placed in a sequence perpendicular to the scanning line detecting different radiation reacting or radiation features. As is apparent from FIG 1, the three detector element rows 7a, 8a, 9a are hit by light from the same line 5 along the carrier 4 because the prism 11a deflects the light from the same line on the carrier 4 to different rows of detector elements extending parallel to the scanning line. The filters 14a, 15a, 16a provided in the light path could make a passband around different wavelength regions, but they could also be polarisation filters and thus transmit light of a certain kind of polarisation. Combination of these kinds of filters are also possible.

It could instead be possible to provide the scanner housing with a detector arrangement in another way than what is described above, for instance over an area

with extension in two dimensions of some kind. The signal from scanning line 5 on the carrier can then be integrated across several detector lines or the detector elements can be shifted the way that are done in TDI-detectors.

The signals from the detector element rows in all the embodiments shown could be stored or directly used for further processing later in a separate computer and/or be used for controlling a process or the like. The samples to be monitored could, for example, be taken at close intervals during a process operation. In this way the process could be controlled on-line.

As illustrated in FIG 13, as the scanning is based upon the movement of the carrier 4 through the scanning device, it easy to combine the scanning device with other units to form a device for the automation of the consecutive monitoring of carriers 4. The complementing units could, for instance, be a carrier stacker 80 which can automatically load carriers in the scanning device 83, and a spot-picker 81 to pick up the spots of gel containing interesting labels 2 of the sample/samples. It will then be possible to monitor a multitude of carriers in an automated, simple and correct way with aspects of the separated labels 2 of the samples 3 in each carrier 4. It will also be possible to automatically pick up interesting labels 2 for later further analysis.

A system for monitoring several carriers of gels or samples in sequence after each other, shown in FIG 13, comprises a stack of carriers 4 having materials to be monitored placed in the carrier stacker 80. The carrier 82 in the lowest position is moved by a carrier feeding means (shown schematically by 88) such as a endless belt, track, rollers or the like, in the carrier stacker to a carrier scanner 83 having illuminating and detecting devices in a housing 85 and optics 86 in fixed positions. The scanning of the carrier is provided by moving it through the scanner 83. The inside of the whole scanner in shielded from ambient light and could also, for example, have black and dull inner walls. A reflector 87 folds the light path in the

same way as in FIG 3. Only one optics 86 is provided common for all arrays of detector elements. The illumination is provided by one or more light sources placed over the emerged object illuminating the carrier in a skew angle from the top. The spot picker 81 could be a separate unit which can be placed after the scanner 83 so that carriers are automatically fed into it from the scanner 83 or the spot picker could be provided in the same casing as scanner 83. The former has the advantage that it is easy to add further analysis units between the scanner and spot picker if required and that both the scanner and spot picker can be moved and used independently of each other if required. The latter has the advantage that the scanner 83 and spot picker 81would share the same frame of reference. This means that if the scanner optics 86 are at a fixed distance x from the spot picker 81, then after a spot of interest has been identified by the optics 86, the spot picker can pick up that spot when the carrier 4 has been sensed as having moved that same distance x towards the spot picker 81.

In a simple embodiment, the spot picker could comprise of a light emitting device which projects a spot of visible light onto the spot which is to be picked up and a human operator then manually picks up the illuminated spot. In a further embodiment, the spot picker could comprise a robot spot picker which is automatically guided to the spot of interest and which has spot picking means for removing the spot from the carrier 4.

Although the invention is described with respect to exemplary embodiments it should be understood that modifications can be made without departing from the scope thereof. Accordingly, the invention should not be considered to be limited to the described embodiments, but defined only by the following claims that are intended to embrace all equivalents thereof.

It is also apparent that even though the radiation sources have been illustrated and described as being light sources, other kinds of radiation providing equivalent effects on the labels 2 of the sample 3 are also usable in the present invention.

CARRIERS CONTAINING TWO-DIMENSIONAL LABELLED MICRO-AREA PATTERNS

Illustrative compounds that causes the label to appear in some micro-areas but not in others have been macromolecules and their fragments, such as proteins, nucleic acids etc. and other bioorganic and/or organic compounds. Low molecular weight compounds, such as haptens, steroid hormones, lipids should be mentioned as examples of other bioorganic/organic compounds.

A carrier exhibiting a two-dimensional pattern of labelled micro-areas may be obtained as a consequence of separation of one or more samples containing a plurality of different labels into labelled micro-areas, such that each such area represents an individual label or a group of labels. The labels may be inherently detectable (inherent labels) or may have been provided with a detectable label (for instance dyed) either before or after the separation.

By separating/transporting the sample labels in two dimensions in the carrier and using different separation principles in each dimension, labelled micro-areas will appear in the carrier surface. Each labelled micro-area will represent a label or a group of labels. The labelled micro-areas will become arranged in a more or less regular pattern having columns initiated by separation in the first dimension and lines initiated by the separation in the second dimension. A typical example is two-dimensional gel electrophoresis in which separation initially is done in the first dimension based on one property, for instance the isoelectric points of the labels, and then in the second dimension on another property, for instance differences in the molecular weights of the labels.

CLAIMS

1. Method for monitoring an essentially planar carrier (4) having at least one kind of label (2), preferable at least two, in micro-areas of the carrier, the labels having different detectable features,
characterised by the step of:
detecting the at least one kind of label in the carrier along at least one line with at least one detector element row (7a,8a,9a;41,42,43;60,61,62;61a) for essentially simultaneous detection of at least two different features of the at least one kind of label.

2. Method according to claim 1, **characterised** by the steps of:
illuminating the carrier along said at least one line with radiation (6a; 6;35 to 40;45;46;47,48;50-52;68a,69a,70a) adapted to provide radiation reaction feature of at least one of said at least one label detectable by said at least one detector element row;
making said detection substantially simultaneously with the illumination; and
providing values of the detected feature of each kind of label separately.

3. Method according to claim 1 or 2, **characterised** in that the separate features are different wavelengths.

4. Method according to anyone of the preceding claims, **characterised** in that the detected features of the labels represent different fluorescing qualities, and that for each kind of label the wavelength of illumination is discriminated from the wavelength of the detected fluoresced quality from the label.

5. Method according to any of the preceding claims, **characterised** by the step of:

moving the carrier and the at least one detector element row together with the illumination in relation to each other such that the carrier is scanned by the at least one detector element row essentially perpendicular to said line or lines.

6. Method according to claim 5, **characterised** by the steps of:
illuminating only one line in the carrier, and
detecting the emitted radiation from that line by a number of parallel detector element rows, each row detecting mutually different features of the emitted radiation

7. Method according to claim 5, **characterised** by the steps of:
illuminating a number of lines in the carrier, and
detecting the emitted radiation from each of said lines by only one detector element row or an individual among a number of parallel detector elements rows, each detection representing a different feature.

8. Method according to claim 6 or 7, **characterised** by the steps of:
illuminating the line(s) simultaneously with different kinds of radiation providing different radiation reaction features of the labels, and
detecting different features of the emitted radiation from the labels by the different detector element rows.

9. Method according to claim 6 or 7, **characterised** by the steps of:
illuminating the lines in sequence with different kinds of radiation providing different radiation reacting features of the labels, and
detecting different features of the emitted radiation from the labels by the at least one detector element rows in the same sequence.

10. Method according to any of the preceding claims, **characterised** by the steps of:

placing the illumination and the at least one detector element row in a fixed arrangement, and by moving a number of carriers in sequence to be scanned by the at least one detector element row.

11. Method according to any of the preceding claims, **characterised** by the steps of: processing signals generated from the detector element rows separately and presenting the results of the processing on at least one display.

12. A device for monitoring an essentially planar carrier having at least one kind of label, preferable at least two, distributed to micro-areas of the carrier, the labels having different radiation reacting features or radiation features, **characterised** by

- illumination or irradiation arrangement (6;35 to 40;45;46;47,48;50 to 52;53;6,84) for providing radiation to at least one line of the carrier;
- detector means (1;31;41,42,43;56;85 to 87) comprising at least one detector element row for detecting at least two of said features in the at least one line in the carrier;
- scanning means for moving said detector element rows and said carrier in relation to each other thereby scanning the carrier.

13. Device according to claim 12, **characterised** by
analysing means (27) for processing the signals received from the at least one detector element row and generating signals representative of the distribution of the at least two detected features from the at least one label in the carrier.

14. A device according to claim 12 or 13, **characterised** in that the different detector element rows are adapted to detect different radiation features.

15. Device according to any of the claims 12 to 14, **characterised** in that the radiation provided by the illumination or irradiation arrangement is adapted to each kind of label present in the carrier.

16. Device according to any of the claims 12 to 15, **characterised** that the analysing means (27) computes the distribution of the different kinds of labels in the carrier substantially simultaneously and presents the distribution for the different kinds of label features separately.

17. Device according to any of the claims 12 to 16, **characterised** in that the scanner means is adapted to move the carrier and have the detector means and the illumination or irradiation arrangement fixed.

18. Device according to any of the claims 12 to 17, **characterised** in that the illumination or irradiation arrangement (6,84) and the scanner means (85 to 87) are placed in a fixed arrangement, and storage and feeding means for carriers enabling sequence feeding of carriers through the fixed arrangement.

19. Device according to any of the claims 12 to 17, **characterised** in that the illumination or irradiation arrangement (30) is located so as to guide the radiation into the carrier through an edge at one side of the carrier.

20. System for monitoring samples in sequence, wherein said system comprises a carrier feeding means (88) and a device (83) of the type according to any of claims 12-19 for monitoring an essentially planar carrier (82), wherein said carrier feeding means (88) is adapted to feed an essentially planar carrier (82) into said device (83).

21. System according to claim 20, **characterised** in that it further comprises a spot picker (81).

22. System in accordance with claim 21, **characterised** in that said spot picker (81) is integrated in the same casing as the monitoring device (83).

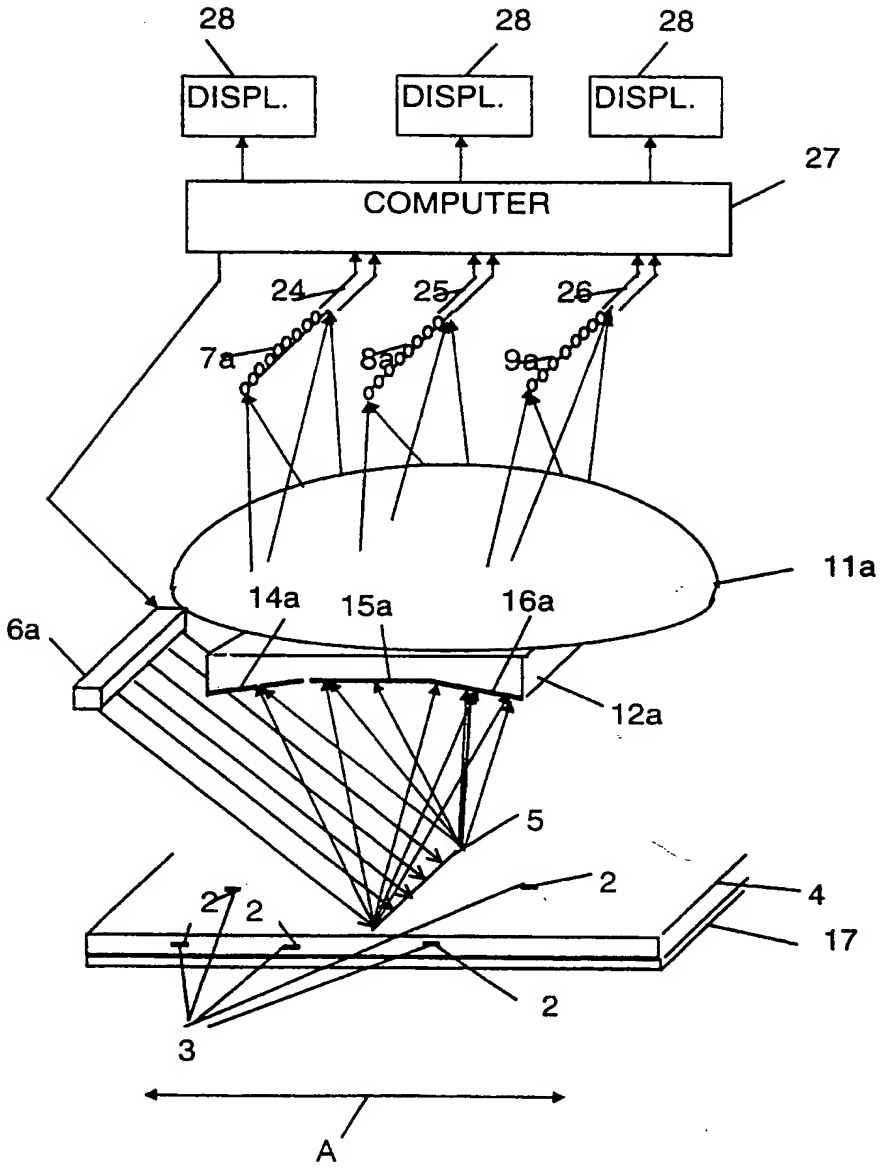
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FIG 1

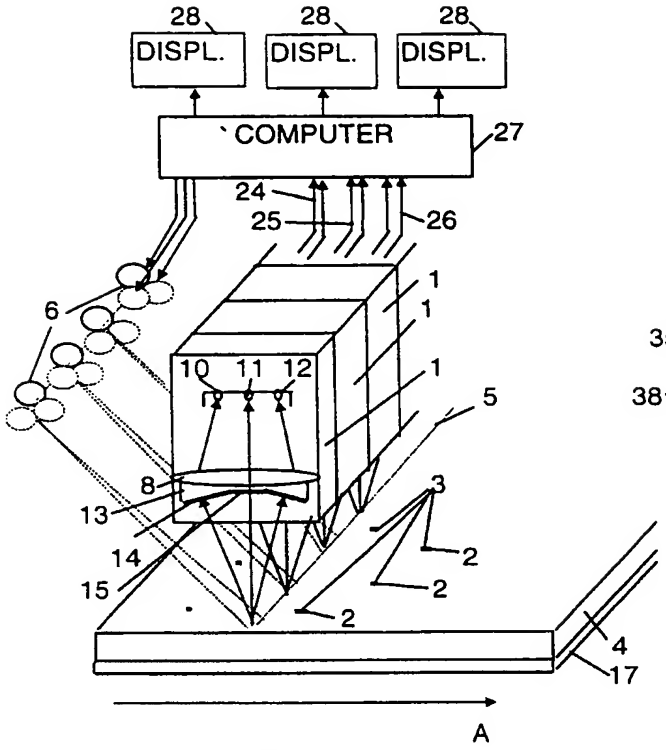

FIG 2

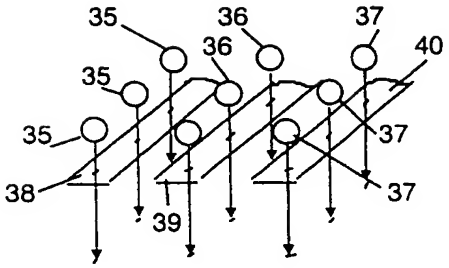

FIG 4

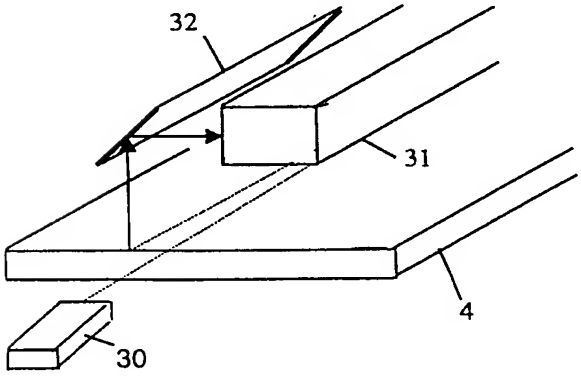

FIG 3

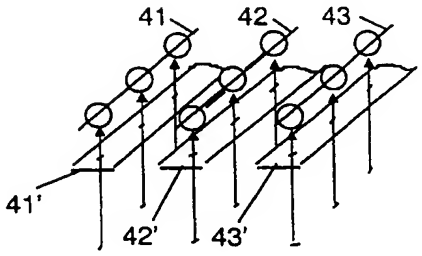

FIG 5

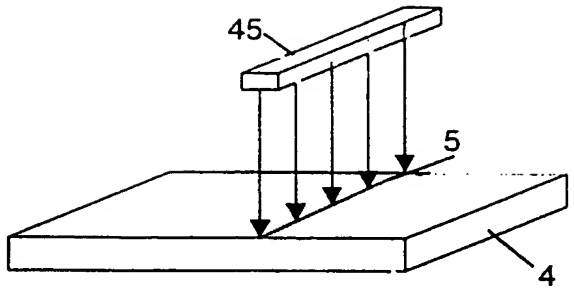

FIG 6

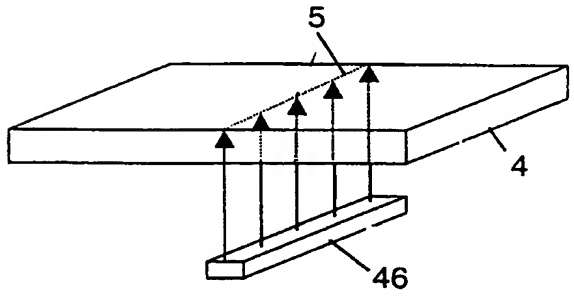

FIG 7

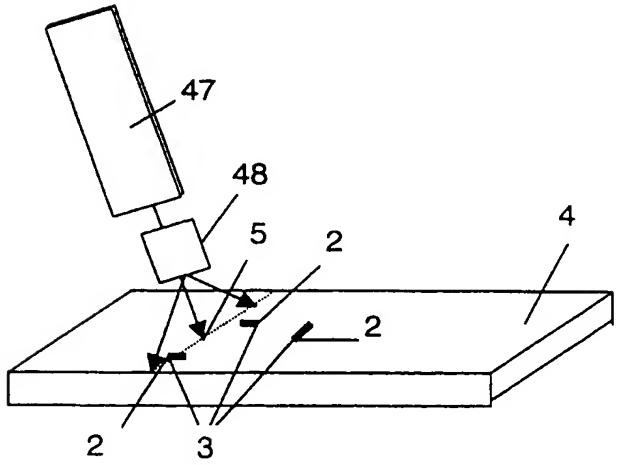

FIG 8

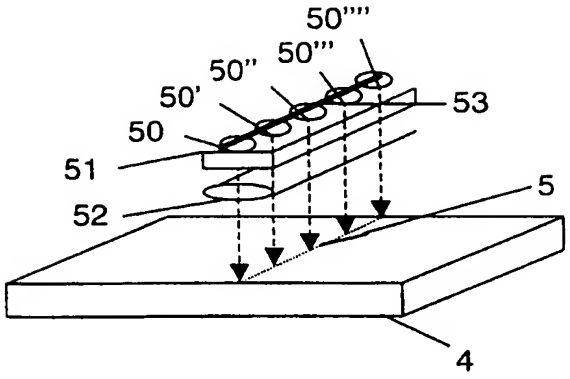

FIG 9

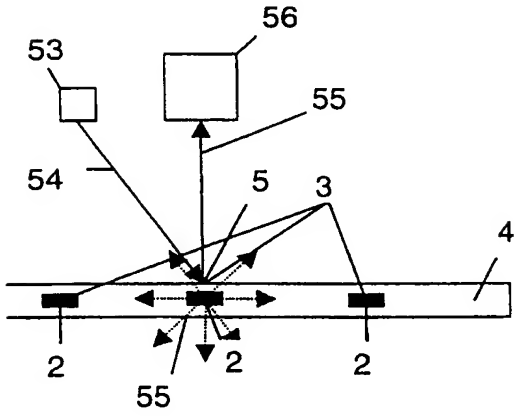

FIG 10

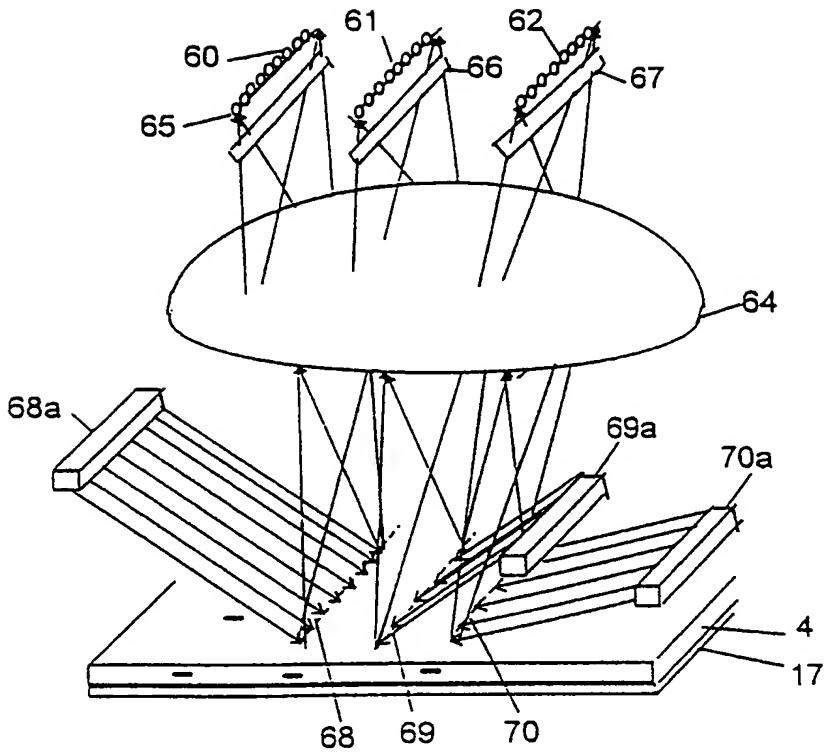

FIG 11A

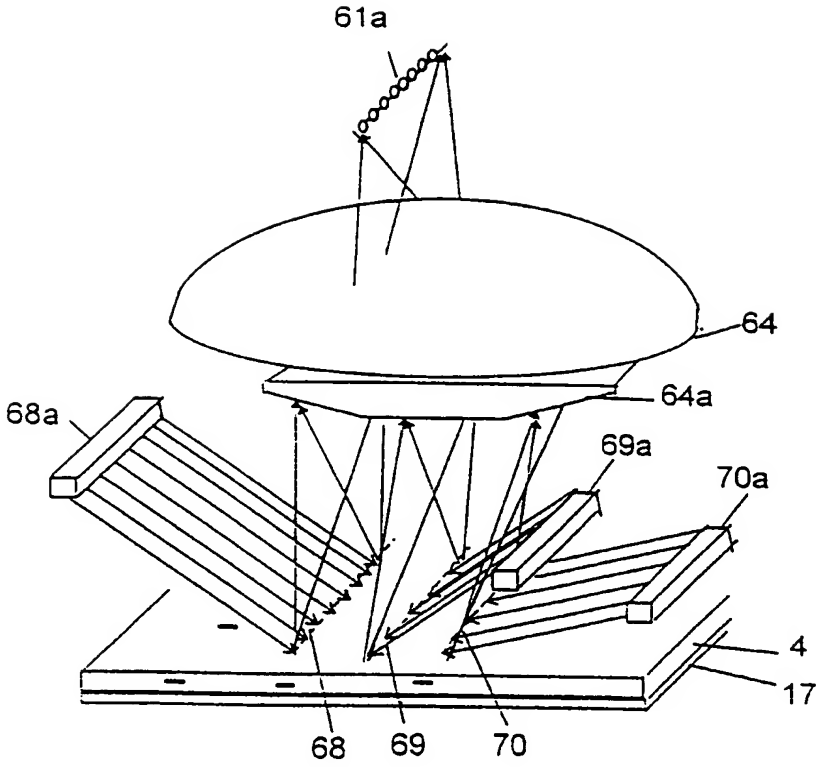

FIG 11B

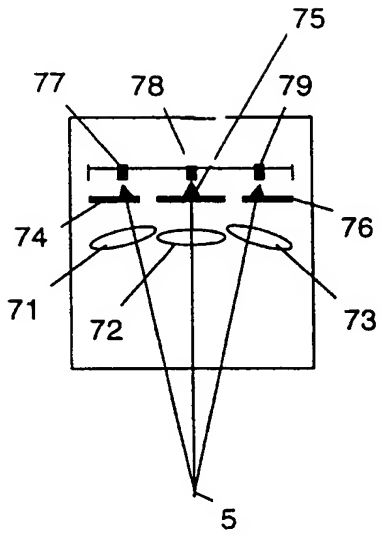

FIG 12

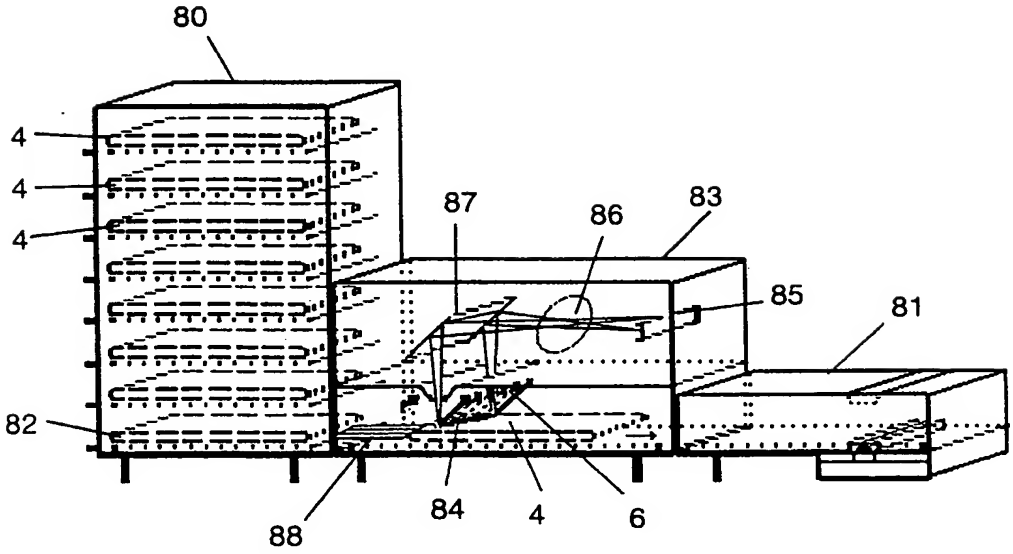

Fig 13

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/10458

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N27/447

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 307 148 A (KAMBARA HIDEKI ET AL) 26 April 1994 (1994-04-26) column 5, line 11 -column 6, line 54; figure 1	1-4,12
Y	WO 95 21377 A (PERKIN ELMER CORP ;HOFF LOUIS B (US); LACHENMEIER ERIC W (US); RAY) 10 August 1995 (1995-08-10) page 5, line 10 -page 7, line 22; figure 2	1-4,12
A	DE 40 11 730 A (HITACHI LTD) 18 October 1990 (1990-10-18) abstract; figure 1	1
A	US 5 162 654 A (KOSTICHKA ANTHONY J ET AL) 10 November 1992 (1992-11-10) abstract; figure 1	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 June 2000	14/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Duchatellier, M

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INTERNATIONAL SEARCH REPORT

Inter...onal Application No
PCT/EP 99/10458

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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A	DE 43 30 741 A (OLYMPUS OPTICAL CO) 17 March 1994 (1994-03-17) abstract	20
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ..nal Application No
PCT/EP 99/10458

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